

REVIEW ARTICLES

A REVIEW OF ENDOBRONCHIAL ULTRASOUND GUIDED TRANSBRONCHIAL NEEDLE ASPIRATE (EBUS-TBNA)

Aslam Khan, Shahid Jamal, Jawad Khaliq Ansari, Arshad Naseem

Army Medical College & National University of Sciences and Technology, Islamabad, Pakistan

INTRODUCTION

Fine-needle aspiration cytology (FNAC) is a method used since long along with different stereotactic guidance. Endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) is a sampling method for patients who have enlarged mediastinal or hilar lymph nodes/masses, detected on computed tomography¹⁻³. Endobronchial ultrasound (EBUS) uses ultrasound along with bronchoscope to visualize airway wall and structures adjacent to it. The clinical application and diagnostic benefits of EBUS have been recognized and EBUS has been assimilated into routine practice in many centers because of its high diagnostic informative value and low risk. In future it is most likely to replace the invasive methods for evaluating mediastinal lymphadenopathy, other lesions and also for staging lung cancer⁴⁻⁵. Other techniques are available for suspected lesions of the mediastinum, including standard flexible bronchoscopy with blind TBNA, transthoracic needle aspiration, mediastinoscopy etc but EBUS-TBNA is least invasive, and has good diagnostic yield for mediastinal pathologies⁷. Hilar nodal stations are difficult to access and may require thoracoscopy and on occasion a thoracotomy. Moreover, these techniques cannot be repeatedly applied on the same patient^{8,9}. Contrary to this, EBUS-TBNA, when combined with EUS (Endoscopic Ultrasound Guided), can sample all the key nodal stations and also can be performed repetitively^{6,10,11}. The start of EBUS-TBNA dates back to early 1990s^{6,12}. At present throughout Pakistan, EBUS-TBNA is being carried out only in a couple of centers (pulmonology department, military hospital being one of them), hence

limited local data and information is available regarding this procedure. The technology is available in two forms: radial EBUS and linear EBUS-TBNA probes.

Radial EBUS

Radial EBUS has a 20-MHz (12e30 MHz available) rotating transducer that can be inserted together with or without a guide sheath through the working channel (2.0-2.8 mm) of a standard flexible bronchoscope. Radial EBUS transducer probes come in different sizes with external diameters of 1.4-2.6 mm. 'Central' probes are utilised with balloon sheaths in the proximal airways for either bronchial wall assessment or to guide TBNA of lymph nodes (Fig-1). Radial EBUS helps to evaluate the airway walls, guide TBNA (diagnostic yield: 72-86%) and diagnose peripheral lung lesions (diagnostic yield: 61-80%).

Linear EBUS-TBNA

The linear EBUS probe has been built into a dedicated flexible bronchoscope to enable real-time TBNA biopsies (Fig-2). This EBUS bronchoscope has an external diameter of 6.9 mm which is larger than a standard flexible bronchoscope. Therefore, oral rather than nasal intubation is necessary. The endoscopic viewing optics is at a 30-degree oblique angle and operator compensation is required when maneuvering the bronchoscope. Particular attention is needed in intubating the trachea and often only the anterior apex of the vocal cords is visible as the scope enters the subglottic space. This bronchoscope has a 2.0-mm working channel that can house a dedicated 22 G biopsy needle. This needle has multiple small dimples on its shaft to enhance echogenicity and improve visualization on the screen. The depth of penetration can be varied from 5 to 40 mm with a safety lock. After endobronchial intubation, the EBUS-TBNA scope is positioned at the approximate location of the target lymph node or paratracheal tumor. Although there is a

Correspondence: Prof Aslam Khan, Army Medical College, Rawalpindi, Pakistan

Email: akhan56258@hotmail.com

Received: 23 April 2015; received revised: 25 June 2015; accepted: 15 July 2015

balloon that can be filled with sterile water or saline to facilitate coupling, but is not always needed. Doppler can be used to assist in making the distinction between lymph nodes and blood vessels. Once the target lymph nodes or tumor is identified, TBNA is performed. The needle sheath is pushed forward such that it is visualized on the endoscopic image before the 'jabbing' technique is used to perform TBNA under real-time guidance (Fig-2). Linear EBUS-TBNA transducers produce real-time TBNA. The reported sensitivity of real-time EBUS-TBNA is 95.08% and the negative predictive value was 93.02%. This diagnostic yield is superior to cervical mediastinoscopy^{13,14}. Visualization of the needle sheath prevents inadvertent puncture of the bronchoscope by the aspiration needle. Once the TBNA needle is within the target, the stylet of the needle is agitated to dislodge any airway debris before being removed for biopsies to be aspirated. For mediastinal staging of non-small cell lung cancer, 3 cytology aspirations per lymph node station is recommended. If an adequate core specimen is obtained, then 2 passes will suffice¹⁵.

Lymph node Stations

Lymphadenopathy can be caused by a variety of conditions. The accurate assessment of lymph node involvement is a pivotal component for both diagnosis and treatment. For the past 40 years, clinical and pathological extent of lymph node disease/involvement has been described using the lymph node maps. The key to assessing treatment outcomes, planning and analyzing clinical trials and deciding therapy for patients requires a universally accepted nomenclature that describes lymph node involvement in detail¹⁶. The first lymph node map was developed by Naruke (1978)¹⁷, during the 1960s, and initially it was widely used (Figure-3)¹⁵. However attempts to improve this map were made by the American Thoracic Society (ATS) and resulted in the formation of the so-called Mountain-Dresler modification of the ATS map (MD-ATS) (Figure-4)^{18,19}.

Significance of EBUS

Computerized Tomography (CT) scan was and remains to be the imaging modality of choice for diagnosis and staging of mediastinal



Figure-1: Radial EBUS transducer probes. 'Peripheral' probe that utilizes guide sheaths without balloons to locate peripheral lung lesions and 'Central' probe that employs balloon sheaths to assess airway walls and identify lymph nodes⁵².

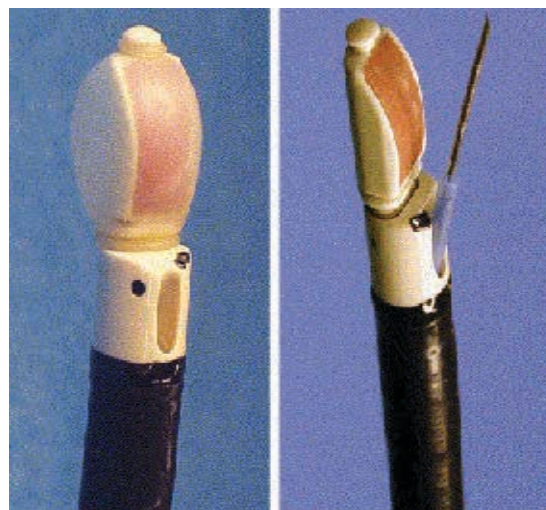


Figure-2: Linear EBUS TBNA bronchoscope with needle protruding through guide sheath⁵².

and lung associated pathologies. However, CT has proved fruitless in evaluation of lymph node involvement and diagnosis of air wall infiltration in case of lung cancer. Positron Emission Tomography-CT (PET-CT) to a certain extent improved the mediastinal lymph node assessment. However, to obtain tissue for histopathology or cytopathology, media-

stinoscopy or thoracotomy is needed, that are quite invasive procedures requiring general anaesthesia. The need for a better imaging modality was increasingly felt essential. In the

widespread acceptance of this innovative and unique method leading to a new era for respiratory physicians²².

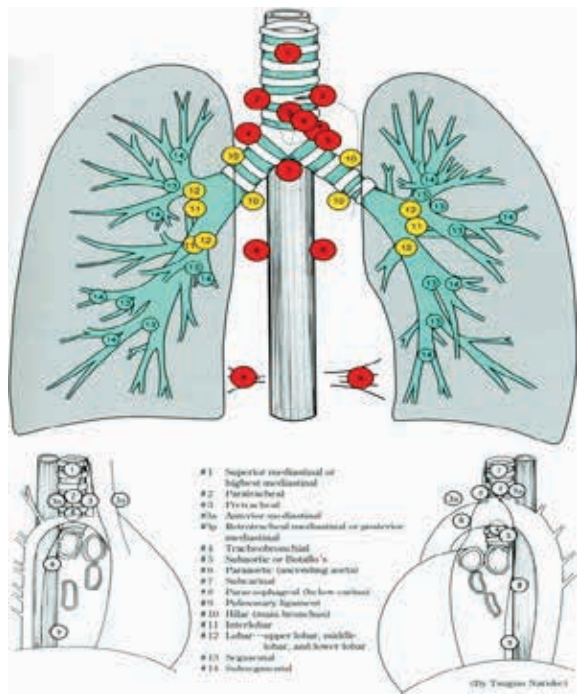


Figure-3: The Naruke lymph node map for the staging of lung cancers¹⁶.

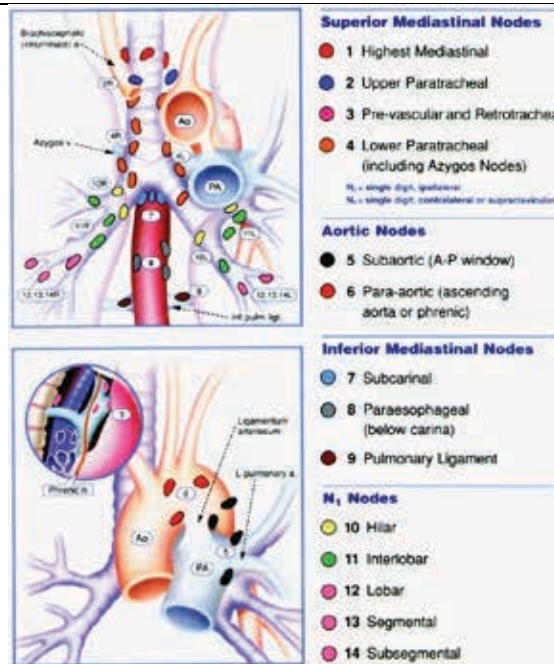


Figure-4: The Mountain-Dresler modification of the lymph node map proposed by the American Thoracic Society¹⁶.

late 1980s endoscopic ultrasound (EUS) was introduced in gastroenterology. However the same could not be used for all mediastinal structures due to interference of air, as air cannot conduct ultrasound waves. After years of dedicated research it was in 1990s that an Endobronchial ultrasound system with balloon catheter was made commercially accessible as Radial probe (RP- EBUS). Initially it was not widely accepted and the topic of discussion for some time was that whether Endobronchial ultrasound is just an expensive toy or a useful tool²⁰. In 2002, a new bronchoscope equipped with a convex type ultrasound probe on the tip was introduced into clinical practice²¹.

In the past decade an increasing number of researchers found EBUS greatly useful in several conditions. The EBUS has become a burning topic and is becoming an indispensable bronchoscopic tool. With the recent introduction of ultrasonic bronchoscope with real time guidance for needle aspiration there is

Indications for EBUS-TBNA

The EBUS-TBNA is useful in several clinical settings for the diagnosis of intrapulmonary and mediastinal tumors, and adenopathies of different etiology, such as sarcoidosis, tuberculosis and lymphomas²¹. Various studies have investigated the initial diagnostic accuracy of EBUS-TBNA in diagnosing both benign and malignant lesions²³. In some of the conditions the diagnostic utility is as follows;

In Sarcoidosis: The diagnosis of sarcoidosis is proven when there is a harmonious clinical/radiological picture, together with pathological evidence of non caseating epithelioid cell granulomata. Sarcoidosis occurs worldwide, in all races, with an average incidence of 16.5 per 100,000 in men and 19 per 100,000 in women²⁴. For the pathological diagnosis of sarcoidosis EBUS-TBNA is said to be an accurate and harmless method. In a

study, the EBUS-TBNA was reported as the most sensitive procedure for diagnosing sarcoidosis and was recommended, to be considered first for the histopathological diagnosis of stage I and stage II sarcoidosis^{25,26}. In another study by Oki et al (2012)²⁷ the diagnostic yield of EBUS-TBNA for sarcoidosis was found to be higher than that for transbronchial lung biopsy.

In diagnosis of tuberculosis: Tuberculosis (TB) remains a global threat with the WHO estimating 9.4 million cases worldwide in 2009. In the pathogenesis of TB mediastinal and hilar lymphadenopathy are well established phenomena. In the present period where the incidence of drug resistant TB is on the rise, obtaining pathological as well as microbiological proof to improve the management of TB has become mandatory. The investigation of suspected cases of intrathoracic TB, is greatly aided by means of aspiration of the intrathoracic lymph nodes and tracheobronchial wall-adjacent lung lesions by using endobronchial ultrasound-guided transbronchial needle aspiration. In a study by Sun et al (2013)²⁸ the sensitivity, specificity, positive and negative predictive values were 85%, 100%, 100% and 75%, respectively. In tuberculous endemic countries like Pakistan, material collected by EBUS-TBNA can also be sent for gene expert to further aid in the diagnosis of TB²⁸. The EBUS-TBNA is a safe and effective first-line investigation in patients with tuberculous intrathoracic lymphadenopathy²⁹.

Neoplastic Lesions

Carcinoma of the lung is without doubt most important cause of cancer related deaths in industrialized countries. Lungs frequently are the site of metastases from cancers arising in extra thoracic organs, however, primary lung cancer is also common. Roughly 95% of primary lung tumors are carcinomas; the remaining 5% mainly include neuroendocrine tumors, mesenchymal malignancies (e.g., fibrosarcomas, leiomyosarcomas), lymphomas, and a few benign lesions. Carcinomas of the lung is classified into two broad groups including, Small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), with the

latter including adenocarcinomas, squamous and large cell carcinomas. The EBUS TBNA helps in real time visualization of the mediastinal/hilar masses, accurate measurement of their size and aspiration of material for TBNA and histopathology⁶.

Role of EBUS in staging of non-small cell lung cancer (NSCLC): Currently available techniques for the initial diagnosis of lung cancer include electromagnetic navigation bronchoscopy with computed tomography mapping and sample collection, endobronchial ultrasound (EBUS) using radial or convex probe tips, and the combination of the two approaches³⁰. In determining the lymph node involvement in cases of NSCLC, EBUS-guided transbronchial needle aspiration (TBNA) has a much better diagnostic yield as compared to conventional TBNA in all lymph node stations except the subcarinal lymph nodes³¹. It has the ability to visualize the airway wall very precisely hence helps to describe the tumor component of staging³². It also aids in planning endobronchial treatment modalities by giving information regarding tumor spread, that is whether the tumor has extended into or beyond the cartilage or is just limited inside the submucosal layers. In combination with endoscopic ultrasound-guided fine-needle aspiration, it can be used to meticulously sample the mediastinal masses³³. In a prospective study, EBUS proved to be superior to CT scan in showing airway involvement by lung cancers³². In differentiating external compression of airways from actual tumor infiltration EBUS has a specificity of 100%, a sensitivity of 89%, and an accuracy of 94% compared to CT, which is far inferior, with a specificity of 28%, a sensitivity of 75%, and an accuracy of 51%³⁴. Radial EBUS probes can be used in cases of advanced tumors to determine the extent and patency of the airways beyond the level of stenosis³⁵. Measuring the length of stenosis and proximity of any blood vessel to the bronchial wall is of immense importance in determining the interventional measures. Studies reveal that EBUS has guided and helped in modification of therapy in 43% of the cases undergoing therapeutic bronchoscopy³⁶.

Lymphomas

The diagnostic accuracy of EBUS-TBNA for lymphomas is low as compared to staging for lung cancer. As the material obtained is small for diagnosis and immunohistochemistry required for diagnosis of Lymphoma. Still it is suggested that in case of isolated lymph node this procedure can be attempted as initial tool³⁷. In a study by Steinfort & Irving (2010)³⁸, the sensitivity, specificity, negative predictive value, and diagnostic accuracy of EBUS-TBNA for the diagnosis of lymphoma were calculated as 86.7%, 100%, 96.4%, and 97%, respectively.

Sarcomatous lesions: Spindle cell lesions are quite diverse, and show great clinical and biological variation. They may be malignant, benign or reactive in nature. The use of EBUS-TBNA for diagnosis of such lesions is relatively limited and a few case reports are available³⁹.

Role in assessment of mediastinal, intrapulmonary and endobronchial lesions: The EBUS has made it possible for the physicians to visualize, sample and diagnose various mediastinal abnormalities⁴⁰ including sarcoidosis⁴¹ and mediastinal lymphoma³⁷. Based on appearance it can characterize the intraparenchymal and endobronchial lesions and also help in establishing the likelihood of malignancy. Pulmonary nodules which cannot be visualized by fluoroscopy are sampled by EBUS TBNA, hence preventing the need for surgical procedures⁴². Radial probe EBUS is a relatively precise tool in the exploration of peripheral pulmonary lesions⁴³.

Endobronchial Therapy

The EBUS provides useful supplementary information during various interventions including resection of endobronchial lesion, stricture dilatation, stenting, laser therapy, and argon plasma coagulation⁴³.

Diagnostic Difficulties of EBUS-TBNA

There are various problems encountered by the histopathologist in diagnosing the lesions on EBUS TBNA. The presence of endobronchial cells is not an uncommon finding on TBNA smears. If these cells are there in abundance there is a chance that it may mask

the original pathology. Crushed endobronchial cells can also mimic the appearance of granulomata therefore making the diagnosis very perplexing. Metaplastic cells if present may look like atypical cells. Particularly if suspecting a metastatic disease in a lymph node and such cell groups are mixed with mature looking lymphocytes, can give the wrong impression of metastatic squamous cell carcinoma and can lead to misinterpretation in establishing the diagnosis. At times, foci of cartilage tissue can also be found while traversing the bronchial cartilage. Presence of mucin pools is another finding which can obscure diagnosis thus making it difficult for the cytopathologist / histopathologist in making an accurate diagnosis. Hence, it is of utmost importance that the cytopathologist /histopathologist should have detailed knowledge of all the structures through which the bronchoscope passes during the TBNA procedure.

Contraindications for EBUS TBNA

There are several contraindications for EBUS-TBNA. Most contraindications are related to the potential for tachycardia, bronchospasm, or hypoxemia. Absolute contraindications include current or recent myocardial ischemia, poorly controlled heart failure, and exacerbation of asthma or chronic obstructive pulmonary disease⁴⁴. Relative contraindications are related to bleeding risk and include anti-platelet agents and anticoagulant therapy, coagulopathy, thrombocytopenia, elevated blood urea nitrogen or serum creatinine⁴⁵.

Complications

Endobronchial guided transbronchial needle aspiration is well tolerated and as safe as conventional bronchoscopy^{12,31}. Pneumo-mediastinum, pneumothorax and haemomediastinum can occur very rarely, but a post-procedure chest radiograph is not usually needed. Major vessel puncture is less likely because of real-time sampling, but is not a problem as previously described with aortic haematoma after conventional TBNA⁴⁶. Some EBUS-TBNA centers intentionally traverse the pulmonary artery for left hilar mass sampling⁴⁷. Infectious complications have rarely been

reported, and bacteraemia is usually asymptomatic and clinically insignificant^{37,48}. Other minor complications of EBUS-TBNA include agitation, cough, and blood at the puncture site. Studies on EBUS-TBNA of peripheral pulmonary nodules with radial probe reported moderate bleeding and pneumothorax^{35,44}. The main adverse effect is damage to the biopsy channel of the bronchoscope. This occurs when the sheath of the dedicated needle is not outside the biopsy channel when the needle is advanced. Recently there have been two reports of infection arising in cystic structures (bronchogenic cysts or thyroid cysts) aspirated by EBUS-TBNA^{49,50}. During one pass performed using the piggyback technique, the patient coughed heavily causing the TBNA needle to break and remain lodged in the bronchial wall⁵¹.

CONCLUSION

The EBUS-TBNA has a wide range of applications. It has become an essential part of our bronchoscopy technique. It has gained an important place in lung cancer staging, often replacing mediastinoscopy. After a training period of 20–30 cases the technique is suitable for all experienced bronchoscopists.

REFERENCES

- Schmitt F, & Barroca H. Possible use and role of molecular techniques in fine-needle aspiration cytology (FNAC) practice. *Diagnostic. Histopathol*, 2011; 17 (7): 286–292.
- Martin HE, Ellis EB. Biopsy by Needle puncture and aspiration. *An Surg* 1930; 62:169-81.
- Cetinkaya E, Gunluoglu G, Ozgul A, Gunluoglu MZ, Ozgul G, Seyhan EC et al. Value of real-time endobronchial ultrasound-guided transbronchial needle aspiration. *Ann. Thorac. Med*, 2011; 6:77–81.
- Hata Y, Sakamoto S, Otsuka H, Sato K, Sato F, Makino T, Takagi K. EBUS-TBNA-related complications in a patient with tuberculous lymphadenopathy. *Intern. Med*, 2013; 52:2553–2559.
- Kang HJ, HwangboB, Lee GK, Nam BH, LeeHS, Kim MS, et al. EBUS-centred versus EUS-centred mediastinal staging in lung cancer: a randomised controlled trial. *Thorax*, 2013; 1-8.
- Yasufuku K, Fujisawa T. Staging and diagnosis of non-small cell lung cancer: Invasive modalities. *Respirology*, 2007; 12(2):173-83.
- Almeida FA. Bronchoscopy and endobronchial ultrasound for diagnosis and staging of lung cancer. *Cleve. Clinic. J. Med*, 2012; 79:eS11–6.
- Medford ARL, Bennett JA, Free CM, Agrawal S. Mediastinal staging procedures in lung cancer: EBUS, TBNA and mediastinoscopy. *Curr. Opin. Pulm. Med*, 2009; 15:334–342.
- Ernst A, Anantham D, Eberhardt R, Krasnik M, Herth FJF. Diagnosis of mediastinal adenopathy-real-time endobronchial ultrasound guided needle aspiration versus mediastinoscopy. *J. Thorac. Oncol*, 2008;3:577–582.
- Yasufuku K. Endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) for the evaluation of the mediastinum. *Japan. J.Thorac. Surg*; 2007; 60: 711–717.
- Choi YR, An JY, Kim MK, Han HS, Lee KH, Kim SW et al. The diagnostic efficacy and safety of endobronchial ultrasound-guided transbronchial needle aspiration as an initial diagnostic tool. *Korean. J. Intern. Med*, 2013; 28: 660–667.
- Herth FJF, Eberhardt R, BeckerHD, ErnstA. Endobronchial ultrasound-guided transbronchial lung biopsy in fluoroscopically invisible solitary pulmonary nodules: A prospective trial. *Chest*, 2006;129:147–150.
- Vincent BD, El-Bayoumi E, Hoffman B, Doelken P, DeRosimo J, Reed C et al. Real-Time Endobronchial Ultrasound-Guided Transbronchial Lymph Node Aspiration. *Ann. Thorac. Surg*, 2008; 85:224–230.
- Groth SS, Whitson BA, D’Cunha J, Maddaus MA, Alsharif M, Andrade RS. Endobronchial ultrasound-guided fine-needle aspiration of mediastinal lymph nodes: a single institution’s early learning curve. *Ann. Thorac. Surg*;2008; 86: 1104–1109.
- Anantham D, Mariko KS, Ernst A. Endobronchial ultrasound Review. *Respiratory Medicine* 2009; 103, 1406-14.
- Rusch VV, Asamura H, Watanabe H, Giroux DJ, Rami-Porta R, Goldstraw P. The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J. Thorac. Oncol*, 2009; 4(5):568–577.
- NarukeT, Suemasu K, Ishikawa S. Lymph node mapping and curability at various levels of metastasis in resected lung cancer. *J. Thorac. Cardiovasc. Surg*, 1978; 76:832–839.
- Tisi GM, Friedman PJ, Peters RM. Clinical staging of primary lung cancer. *Am. J. Respir. Crit. Care. Med*, 1983; 127:659–664.
- Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. *Chest*, 1997; 111:1718–1723.
- Becker, HD. EBUS: A New Dimension in Bronchoscopy. *Respiration*, 2006; 73(5):236–242.
- Nakajima. T, Yasufuku.K, Yoshino I. Current status and perspective of EBUS-TBNA. *Gen Thorac Cardiovasc Surg* 2013; 61: 390–96.
- James, D. G. (2000). A clinicopathological classification of granulomatous disorders. *Postgrad. Med. J*; 76(898):457–465.
- Choi YR, An JY, Kim MK, Han HS, LeeKH Kim SWet al. The diagnostic efficacy and safety of endobronchial ultrasound-guided transbronchial needle aspiration as an initial diagnostic tool. *Korean. J. Intern. Med*, 2013; 28(6):660–667.
- Cetinkaya E, Seyhan EC, Ozgul A, Gencoglu A, OzgulG, Cam E et al. Efficacy of convex probe endobronchial ultrasound (CP-EBUS) assisted transbronchial needle aspiration for mediastinal staging in non-small cell lung cancer cases with mediastinal lymphadenopathy. *Ann. Thorac. Cardiovasc. Surg*, 2011; 17(3):236–242.
- Vaidya PJ, Kate AH, Chhajer PN. Endobronchial ultrasound-guided transbronchial needle aspiration: The standard of care for evaluation of mediastinal and hilar lymphadenopathy. *J. Cancer. Res. Ther*, 2013; 9(4):549-551.
- Navani N, Booth HL, Kocjan G, Falzon M, Capitanio A, Brown JM et al. Combination of endobronchial ultrasound-guided transbronchial needle aspiration with standard bronchoscopic techniques for the diagnosis of stage I and stage II pulmonary sarcoidosis. *Respirology*, 2011; 16(3):467–472.
- Oki M, Saka H, Kitagawa C, Kogure Y, Murata N, Ichihara S et al. Prospective study of endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes versus transbronchial lung biopsy of lung tissue for diagnosis of sarcoidosis. *J. Thorac. Cardiovasc. Surg*, 2012; 143(6):1324–1329.
- Sun J, Teng J, Yang H, Li Z, Zhang J, Zhao H et al. Endobronchial ultrasound-guided transbronchial needle aspiration in diagnosing intrathoracic tuberculosis. *Ann. Thorac. Surg*, 2013; 96(6):2021–2027.
- Bodmer T, StrohleA. Diagnosing Pulmonary Tuberculosis with the Xpert MTB/RIF Test. *J Vis Exp*. 2012; (62): 3547.
- Navani N, Nankivell M, Woolhouse I, Harrison RN, Munavvar M, Oltmanns U et al. Endobronchial ultrasound-guided transbronchial needle aspiration for the diagnosis of intrathoracic lymphadenopathy in patients with extrathoracic malignancy: a multicenter study. *J. Thorac. Oncol*, 2011; 6(9):1505–1509.
- Kurimoto N, Fielding DIK, Musani AI. An overview of Endobronchial ultrasonography. *Endobronchial Ultrasonography* 1st ed. Wiley-Blackwell 2011; 1-15.
- Herth F, Becker HD, Ernst A. Conventional vs Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration: A Randomized Trial. *Chest*, 2004; 125(1):322–325.
- Herth F, Ernst A, Schulz M, Becker H. Endobronchial ultrasound reliably differentiates between airway infiltration and compression by tumor. *Chest*, 2003; 123:458–462.
- Herth FJ, Krasnik M, Kahn N, Eberhardt R, Ernst A. Combined endoscopic-endobronchial ultrasound-guided fine-needle aspiration of mediastinal lymph nodes through a single bronchoscope in 150 patients with suspected lung cancer. *Chest*. 2010;138(4):790-4.
- BalamughesT, Herth FJ. Endobronchial ultrasound: A new innovation in bronchoscopy. *Lung India*, 2009; 26: 17–21.

36. Herth FJF, Becker HD, Ernst A. Aspirin does not increase bleeding complications after transbronchial biopsy. *Chest*, 2002; 122:1461-1464.
37. Falcone F, Fois F, & Grosso D. Endobronchial ultrasound. *Respiration*, 2003;70(2):179-194.
38. Steinfurt DP, Irving LB. Patient satisfaction during endobronchial ultrasound-guided transbronchial needle aspiration performed under conscious sedation. *Respiratory Care* 2010; 55(6):702-706.
39. Senturk A, Babaoglu E, Kilic H, Hezer H, Dogan HT, Hasanoglu HC et al. Endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of lymphoma. *Asian Pac J Cancer Prev*, 2014; 15(10): 4169-73.
40. Shingyoji M, Ikebe D, Itakura M, Nakajima T, Itami M, Kimura H, et al. Pulmonary artery sarcoma diagnosed by endobronchial ultrasound-guided transbronchial needle aspiration. *Ann Thorac Surg*, 2013; 96(2): e33-5.
41. Yasufuku K, Nakajima T, Fujiwara T, Yoshino I, Keshavjee S. Utility of endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of mediastinal masses of unknown etiology. *Ann. Thorac. Surg*, 2011; 91(3): 831-836.
42. Garwood S, Judson MA, Silvestri G, Hoda R, Fraig M, Doelken P. Endobronchial ultrasound for the diagnosis of pulmonary sarcoidosis. *Chest* 2007; 132(4): 1298-1304.
43. Herth FJF, Eberhardt R, Vilmann P, Krasnik M, Ernst A. Real-time endobronchial ultrasound guided transbronchial needle aspiration for sampling mediastinal lymph nodes. *Thorax*, 2006; 61(9):795-798.
44. Steinfurt DP, Khor YH, Manser RL, Irving LB. Radial probe endobronchial ultrasound for the diagnosis of peripheral lung cancer: systematic review and meta-analysis. *Eur. Respir. J*, 2011; 37(4):902-10.
45. Wahidi MM, Rocha AT, Hollingsworth JW, Govert JA, Feller-Kopman D & Ernst, A. Contraindications and safety of transbronchial lung biopsy via flexible bronchoscopy: A survey of pulmonologists and review of the literature. *Respiration*, 2005; 72(3):285-295.
46. Ernst A, Eberhardt R, Wahidi M, Becker HD, Herth FJF. Effect of routine clopidogrel use on bleeding complications after transbronchial biopsy in humans. *Chest*, 2006; 129(3):734-737.
47. Agli LL, Trisolini R, Burzi M, Patelli M. Mediastinal hematoma following transbronchial needle aspiration. *Chest*, 2002; 122(3):1106-7.
48. Vincent B, Huggins JT, Doelken P, Silvestri G. Successful real-time endobronchial ultrasound-guided transbronchial needle aspiration of a hilar lung mass obtained by traversing the pulmonary artery. *J. Thorac. Oncol*, 2006; 1(4):362-364.
49. Steinfurt DP, Johnson DF, Irving LB. Infective complications from endobronchial ultrasound-transbronchial needle aspiration. *Eur Respir J* 2009; 34: 524-5.
50. Haas AR. Infectious complications from full extension endobronchial ultrasound transbronchial needle aspiration. *Eur Respir J* 2009; 33: 935-8.
51. Fielding D, Bashirzadeh F, Nguyen P, Hodgson A, James D. . Review of the role of EBUS-TBNA for the pulmonologist, including lung cancer staging. *Thoracic Cancer* 2010; 1: 44-52.
52. Yasufuku K, Chiyo M, Koh E, Moriya Y, Iyoda A, Sekine Y, et al. Endobronchial ultrasound guided transbronchial needle aspiration for staging of lung cancer. *Lung Cancer* 2005; 50(3): 347-54.